REMARKS

Claims 11-18 are pending in the instant application. Claims 11-18 have been rejected. As a preliminary matter, claim 19 has been added to recite specific embodiments of the present invention. Support for claim 19 is found at page 12, lines 26-29. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of the following remarks.

I. Rejection of Claims Under 35 U.S.C. §112

Claims 11-18 have been rejected under 35 U.S.C. 112, first paragraph, as failing to meet the written description requirement. It is suggested that the claims and specification fail to provide adequate written description for the genera of claimed inhibitory agents. It is suggested that the specification does not provide a core structure of inhibitory agents and that because the prior art, as evidenced by Joshi et al. ((2002) *J. Virol.* 76:6545-6557), suggests a lack of homology in agents that bind with high affinity to the reverse transcriptase region of HIV-1, Applicants have not shown possession of the entire claimed genus of inhibitory agents. In response to Applicants arguments filed in the prior response, the Examiner suggests that the teachings of Joshi are relevant to the identification of an aptamer targeted to HIV reverse transcriptase and suggest that sequences that bind with high affinity lack primary sequence homology to each other. Applicants respectfully traverse this rejection.

At the outset, Applicants respectfully believe that the Examiner has not fully taken into consideration Applicants'

arguments filed January 18, 2007 as they relate to this rejection.

MPEP 707.07(f) indicates that "[i]n order to provide a complete application file history and to enhance the clarity of the prosecution history record, an examiner must provide clear explanations of all actions taken by the examiner during prosecution of an application. Where the requirements are traversed, or suspension thereof requested, the examiner should make proper reference thereto in his or her action on the amendment. *Where the applicant traverses any rejection, the examiner should, if he or she repeats the rejection, take note of the applicant's argument and answer the substance of it*" [emphasis added]. No such note or answer to the substance of Applicants' arguments is of record.

As Applicants have previously pointed out, the claims and the specification at pages 8-17 clearly set forth the dumbbell structure of the instant composition, wherein loops (*i.e.*, Y_1 and Y_2 of Formula I) composed of ribonucleic acid or 2',5'-linked ribonucleic acid are combined with stems (*i.e.*, X_1 and X_2 of Formula I) to produce a ligand with a distinct structure which effectively binds and inhibits the RNase H activity of a retroid virus reverse transcriptase. In addition, Applicants have clearly disclosed and directly recite in the claims the 5'-UUYG-3'/2' tetraloop sequence, which is <u>essential</u> to the recognition and binding of the inhibitory agent to the RNase H domain. Indeed, mutating the loop region sequence of UUCG to UACG completely abolishes inhibitory activity. See page 22, lines 25-27. Thus, not only have Applicants provided and claimed a distinct structure (*i.e.*, Formula I) and its essential recognition

sequence (*i.e.*, 5'-UUYG-3'/2'), but pages 14-17 and 20-23 provide multiple examples of sequences, lengths, and base compositions which can be used in accordance with the instant composition.

Therefore, while Applicants have provided objective evidence in rebuttal of this rejection under 35 U.S.C. 112, first paragraph, the Examiner has responded by merely providing a justification of citing Joshi et al. as being relevant to the present invention. However, Applicants respectfully submit that the Examiner's line of reasoning, indicating that "sequences that bind with high affinity lack primary sequence homology to each other" and therefore Applicants have not adequately disclosed the broad genus of inhibitory agents, is scientifically flawed. Because ligand inhibitors exhibit differences in their primary sequence does not preclude their having motifs in common, as well as similarities in secondary and tertiary structures. Indeed, Joshi et al. teach that the three-dimensional structures of all HIV-1 reverse transcriptase inhibitors recognize the same surface on reverse transcriptase and have the potential to form pseudoknot-like secondary structures. See page 6545, paragraph spanning column 1 and 2. Joshi et al. further illustrate that the anti-HIV-1 RT aptamers provided therein exhibit a pseudoknot secondary structure (see Figure 1 at page 6546). Thus, as with the ligands described by Joshi et al., Applicants provide secondary structural characteristics of the instant inhibitory agent, depicted in Formula I as having loops and stems, which are respectively required for recognition/binding and grasping/positioning of the inhibitory agent in the RNase H domain. See page 23, lines 1-9.

In accordance with MPEP §2163, Applicants have disclosed and claim a core sequence (*i.e.*, SEQ ID NO:1), structure (*i.e.*, Formula I), binding specificity (*i.e.*, binding to the RNase H domain of retroid virus reverse transcriptase) and length (X_1 is 2 to 24 nucleotides in length, X_2 is 2 to 24 nucleotides in length, Y_1 is 2 to 8 nucleotides in length, Y_2 is 2 to 8 nucleotides in length) of the instant composition. Moreover, Applicants have provided multiple species of the claimed genus which demonstrate that Applicants were in possession of the claimed invention at the time of filing the present application. As such, the written description requirement under 35 U.S.C. 112, first paragraph, has been met. It is therefore respectfully requested that this rejection be reconsidered and withdrawn.

II. Rejection of Claims Under 35 U.S.C. §103

Claims 11-18 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Wasner et al. in view of Hannoush et al. and in further view of Ray et al. and Clusel et al. The Examiner suggests that Wasner et al. teach a nucleic acid compound for inhibiting the RNase H activity of a retroid virus reverse transcriptase comprising two complementary strands 18-23 nucleotides in length, wherein the strands can be RNA or DNA or both and further wherein the duplex comprise 3′,5′-linked or 2′,5′-linked RNA. It is suggested that Wasner et al. teach that hairpin aptamers designed with the proper 2′,5′ RNA and complementary RNA segments may inhibit the removal of the RNA component of the RNA:DNA hybrid formed during reverse transcription. The Examiner further suggests that Hannoush et al. teach that hairpin structure comprising tetranucleotide loops are

extremely stable and are important structural motifs for the design of nucleic acid aptamers. Clusel et al. is suggested to teach double stranded dumbbell oligonucleotides having increased stability because of the incorporation of hairpin loops at the ends of the duplex structures. The Examiner suggests that Ray et al. teach that peptide nucleic acids are synthetic molecules that can bind with high sequence specificity to a chosen target in a gene sequence and hybrid nucleic acid complexes containing a peptide nucleic acid exhibit extreme thermal stability and unique ionic strength. The Examiner concludes that it would have been obvious to one of skill in the art to incorporate the hairpin loops at both ends of an aptamer, as taught by Clusel et al., incorporate tetranucleotide loops as taught by Hannoush et al., and further incorporate PNAs to further increase the duplex stability as taught by Ray et al. Applicants respectfully traverse this rejection.

Under 35 U.S.C. §103, the factual inquiry into obviousness requires a determination of: (1) the scope and content of the prior art; (2) the differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) secondary considerations. *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966).

As specifically indicated at page 7479, first full paragraph of column 1, Wasner et al. provides an analysis of the unusual RNA binding specificity of 2′,5′-RNA and the properties of RNA:2′,5′-RNA hybrid duplexes, including susceptibility of these duplexes to hydrolysis by RNase H enzymes from *E. coli* and HIV-1 reverse transcriptase. As acknowledged by the Examiner, Wasner et al. teach duplexes composed of two complementary strands 18-23

nucleotides in length (see Table 1). Wasner et al. demonstrate that these 18-23 nucleotide hybrids could inhibit the RNase H activity of HIV-1 reverse transcriptase (see the paragraph spanning columns 1 and 2 at page 7485). However, it is of particular note that Wasner et al. do not teach recognition or binding of a 4 nucleotide molecule or a duplex having the sequence UUCG.

Hannoush et al. provide an analysis of the structural stability of hairpins containing 2',5'-linked RNA loops. Specifically, this reference teaches that hairpins with a UUCG tetraloop are stable, independent of the hairpin stem composition. However, Hannoush et al. do not provide any teaching or suggestion that the UUCG loop sequence is essential for recognition and binding to an RNase H domain of a retroid virus reverse transcriptase.

As indicated in the declaration by Dr. Masad Dahma, submitted herewith, the dumbbells of the present invention have a different structure, sequence, and recognition sequence length (*i.e.*, the four nucleotide tetraloop sequence of UUCG) than the molecules provided by Wasner et al. Given that the RNase H domain requires a minimum duplex length of 8-9 bp for cleavage, it was unexpected that a four nucleotide tetraloop-containing molecule could selectively inhibit RNase H.

"When the PTO shows prima facie obviousness, the burden then shifts to the applicant[s] to rebut." *In re Mayne*, 104 F.3d 1339, 1342, 41 USPQ2d 1451, 1454 (Fed. Cir. 1997). "Such rebuttal or argument can consist of a comparison of test data showing that the claimed compositions possess unexpectedly improved properties or properties that the prior art does not have..." *In re Dillon*,

919 F.2d 688, 692-93, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990)(en banc).

Moreover, even if one were to combine the UUCG sequence of Hannoush et al. with the duplexes of Wasner et al. and further produce dumbbells as in Clusel et al., it could not have been predicted that such a structure would be selective for the RNase H activity of retroid virus reverse transcriptase because most inhibitors of reverse transcriptase inhibit polymerase activity or both the RNase H and polymerase activity of reverse transcriptase. See paragraph 3 of Dr. Masad Dahma's Declaration and the last paragraph of column 2 at page 11983 of Wisniewski et al. ((2000) *Proc. Natl. Acad. Sci. USA* 97:11978-11983; enclosed as Exhibit A). Indeed, Hannoush et al. do not even suggest that the compounds disclosed therein would have any inhibitory activity at all, let alone exhibit specific inhibitory activity against the RNase H activity of HIV reverse transcriptase.

The combined teachings of the references simply do not disclose or suggest the claimed invention. Based on the three-dimensional structure and essential four nucleotide recognition and binding sequence (*i.e.*, UUYG), Applicants fail to see how one of ordinary skill in the art would somehow conclude that the teachings of Wasner et al. would direct the skilled artisan to seek the UUCG tetraloop of Hannoush et al., the dumbbell of Clusel et al. and the peptide nucleic acid of Ray et al. with a reasonable expectation of successfully producing an inhibitory agent which selectively inhibits the RNase H activity of a retroid virus reverse transcriptase. *See KSR Int'l. Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1741, 82 USPQ2d 1385, 1396 (2007) *See also, In re Fritch*, 972 F.2d 1260, 1266, 23 USPQ2d

1780, 1783 (Fed. Cir. 1992) ("The mere fact that the prior art may be modified in the manner suggested by the Examiner [is not sufficient to show obviousness.]").

Because the cited references, when combined, fail to teach or suggest the present invention, these references cannot be held to make the present invention obvious under 35 U.S.C. 103(a). It is therefore respectfully requested that this rejection be reconsidered and withdrawn.

III. Conclusion

The Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

Jane Massey Licata
Registration No. 32,257

Date: **July 16, 2007**

Licata & Tyrrell P.C.
66 E. Main Street
Marlton, New Jersey 08053

(856) 810-1515